How to Recognize Newly Defined Primary Immunodeficiency Disorders in the Allergy Clinic

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Learning Objectives

Upon completion of this session, participants should be able to:

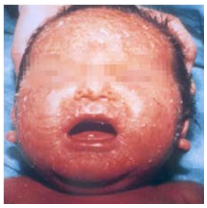
- Recognize the presenting history and physical findings of a selected group of more recently defined primary immune deficiency disorders
- Apply the appropriate diagnostic approaches required to establish the diagnosis of these selected primary immune deficiency disorders
- Discuss the current therapeutic options for managing patients with these selected primary immune deficiencies and the immunologic basis for these defects in host defense

Primary Immune Deficiency Disorders (PIDDs) that Share Selected Findings of Atopy

New Understanding of these Disorders Based on their Underlying Molecular Defects

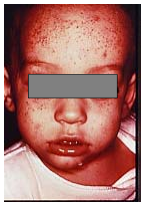
Classic PIDDs Associated with Elevated IgE Levels and Eczema

1) Omenn Syndrome



SCID variant – "leaky" defect affecting RAG1/2, IL7Rα, cγ, ADA

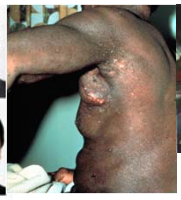
2) Wiskott Aldrich Syndrome



Defect in WASP with triad of eczema, thrombocytopenia and immune deficiency

3) Job's Syndrome (Hyper IgE Syndrome)

Typical facies

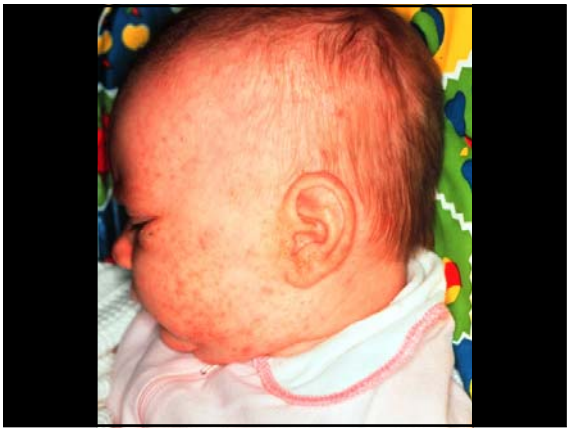


Boils

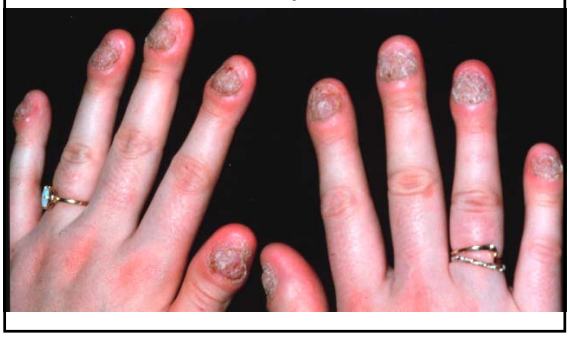
So Satan went forth from the presence of the Lord, and smote Job with sore boils from the sole of his foot unto his crown.
Job II:7

Features of Job's Syndrome

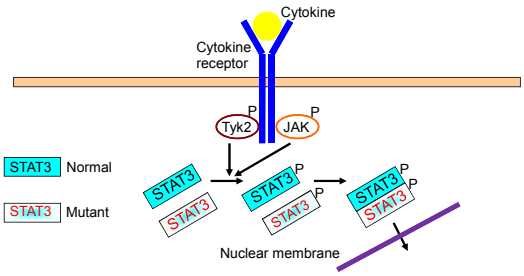
- Atopic features
  - **Elevated IgE and eczema 100%**
- Infectious complications
  - Skin boils ~85%
  - Pneumonias ~85%
  - **Lung cysts (pneumatoceles) ~75%**
  - **Mucocutaneous candidiasis ~85%**
- Prominent somatic features
  - Characteristic facies (>16y) ~100%
  - Scoliosis (>16y) ~75%
  - Delayed dental deciduation ~70%
  - Pathologic fractures ~55%



Candida albicans onychomycosis in Job's Syndrome



Heterozygous Mutation in STAT3 Results in Job's Syndrome

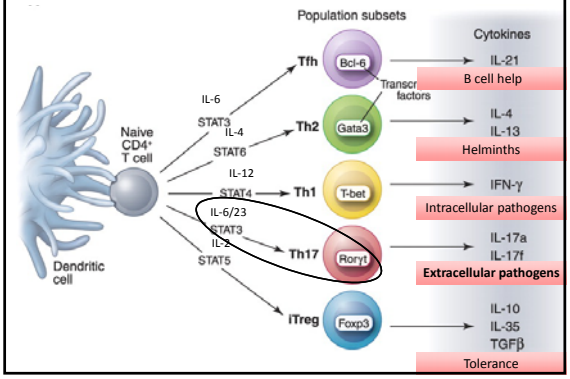


The mutation in STAT3 acts as a dominant negative mutation interfering with DNA transcription normally induced by the binding of the cytokine

Job's Syndrome Conclusions

- Heterozygous STAT3 mutations underlie both dominant and sporadic forms
- STAT3 mutations result in dysregulation of cytokine production and signaling
  - Upregulation of proinflammatory cytokines
  - Underlining basis of ↑IgE remains undefined
  - Compromised generation of a Th17 response
- Definitive diagnosis: mutation testing

Helper T cell Cytokine Production



4) Disease with Elevated IgE Different from Job's Syndrome

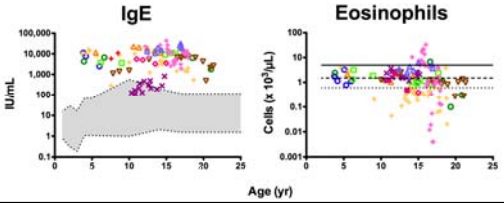
- An autosomal recessive PIDD with elevated IgE was described in 2004 (J Peds 144:93)
- Clinical phenotype differed significantly from Job's Syndrome
  - Lack of pneumatoceles
  - No skeletal or dental abnormalities
  - Different infectious phenotype

Further Characterization of This New AR ↑IgE PIDD

- Zhang et al. (N Engl J Med 361:2046, 2009): combined immune deficiency (11 pts) with ↑IgE resulting from mutations in the gene for the dedicator of cytokinesis 8 (DOCK8 - a guanine nucleoside exchange factor)
- Engelhardt et al. (JACI 124:1289, 2009): "hyper-IgE syndrome" involving large deletions & point mutations in the gene encoding DOCK8 (19 pts)
- DOCK8 appears to be involved in modulating signals that trigger cytoskeletal reorganization

Clinical Phenotype of DOCK8 Deficiency Includes Atopy

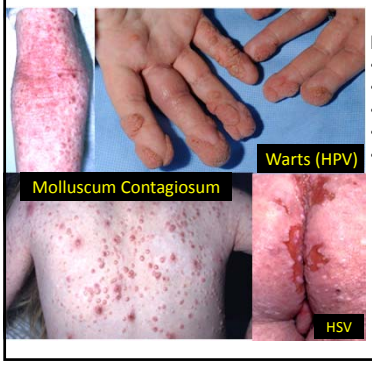
- Atopic dermatitis (~90%)
- Asthma (~45%)
- Allergies (~65%) including food allergy



Clinical Phenotype in DOCK8 Deficiency: Infections

- Viral Infections (~90%)
  - HPV-associated flat and verrucous warts (~30%)
  - Orolabial, anogenital, corneal HSV (~50%)
  - Molluscum contagiosum virus (~40%)
  - Severe varicella or herpes zoster (~20%)
- Other infections
  - Respiratory tract infections (>90%)
  - Bacterial skin infections (~80%)
  - **Mucosal or nail candidiasis (~70%)**

DOCK8 Deficiency



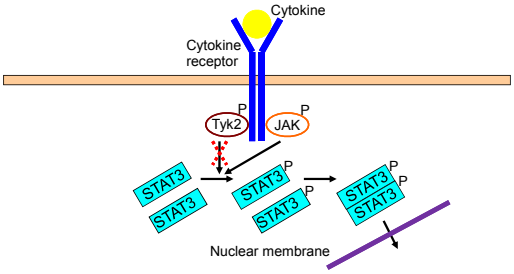
Laboratory findings:
- **High IgE**
- High IgG, IgA
- **Low IgM**, IgA
- Eosinophilia
- **Lymphopenia** (CD4> CD8>NK cell>B cell)

Diagnosis:
- DOCK8 immunoblot
- Array CGH
- Mutation analysis (?) 46-48 exons, 250kB

Summary DOCK8 Deficiency

- Represents a combined immune deficiency
- Basis for atopy remains to be defined
- Cutaneous infections are extremely difficult to treat and often are disfiguring
- High incidence of malignancy: squamous cell CA (~15%) and lymphoma (~10%)
- Immune reconstitution may be the most appropriate therapeutic approach but the data are premature in terms of outcome

5) There Is More: AR Syndrome of ↑ IgE Due to a Defect in Tyk2

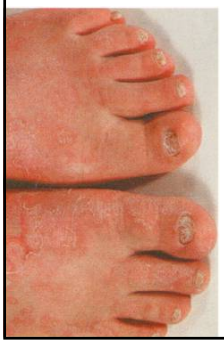


Diminishes the response of Tyk2 dependent cytokine signaling: PIDD with bacterial and viral infections (Minegishi Y, et al Immunity 2006 25:745)

A New PIDD Chapter is Defined

Chronic Mucocutaneous Candidiasis (CMC)

What Do We Know About CMC



It is seen with:
- Job Syndrome (STAT3 defect)
- Tyk2 deficiency
- DOCK8

Could there be a link between the above disorders and CMC seen in:
- APECED (APS-1, AIRE defect)
- Autosomal CMC
- Sporadic CMC

What Is Common in Job's Syndrome and Tyk2 Deficiency (± DOCK8 Deficiency)

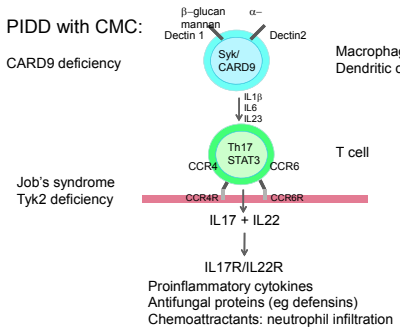
- Dysregulated cytokine production and responses, other than CMC the pattern of infections vary
- Diminished Th17 cell generation most prominent in Job's and Tyk2 deficiency
- Th17 dysfunction could represent a common link for candida susceptibility

A Possible Additional Link of the Th17 Pathway to CMC

A Homozygous *CARD9* Mutation in a Family with Susceptibility to Fungal Infections

Erik-Oliver Glocker, M.D., Andre Hennigs, Mohammad Nabavi, M.D., Alejandro A. Schäffer, Ph.D., Cristina Woellner, M.Sc., Ulrich Salzer, M.D., Dietmar Pfeifer, Ph.D., Hendrik Veelken, M.D., Klaus Warnatz, M.D., Fariba Tahami, M.Sc., Sarah Jamal, M.Sc., Annabelle Manguiat, M.Sc., Nima Rezaei, M.D., Ali Akbar Amirzargar, M.D., Alessandro Plebani, M.D., Nicole Hannesschläger, B.Sc., Olaf Gross, Ph.D., Jürgen Ruland, M.D., and Bodo Grimbacher, M.D.

Immune Response to *Candida* Species



The Connection Between Th17 and CMC Grows Stronger

Brief Definitive Report

Autoantibodies against IL-17A, IL-17F, and IL-22 in patients with chronic mucocutaneous candidiasis and autoimmune polyendocrine syndrome type I

Anne Puel[1,2], Rainer Döffinger[3], Angels Natividad[1,2], Maya Chrabieh[1,2], Gabriela Barcenas-Morales[4], Capucine Picard[1,2,5], Aurélie Cobat[1,2], Marie Ouachée-Chardin[6], Antoine Toulon[2,6], Jacinta Bustamante[1,2], Saleh Al-Muhsen[9], Mohammed Al-Owain[10], Peter D. Arkwright[11], Colm Costigan[12], Vivienne McConnell[13], Andrew J. Cant[14], Mario Abinun[14], Michel Polak[2,15], Pierre-François Bougnères[16], Dinakantha Kumararatne[3], László Marodi[17], Amit Nahum[18], Chaim Roifman[18], Stéphane Blanche[2,7], Alain Fischer[2,7,19], Christine Bodemer[2,6], Laurent Abel[1,2,20], Desa Lilic[21], and Jean-Laurent Casanova[1,2,7,20]

J Exp Med 2010 207:291-297

High titer neutralizing autoantibodies against IL-17A, 17F and/or 22 in the sera of all 33 APS1 pts tested suggests that these autoantibodies underlie chronic mucocutaneous candidiasis

Th17 Function in Host Defense to Candida Becomes Even More Clear

Chronic mucocutaneous candidiasis in humans with inborn errors of interleukin-17 immunity*

Anne Puel,[1*] Sophie Cypowyj,[2*] Jacinta Bustamante,[1] Jill F. Wright,[3] et al

Science 2011; 332:65-68

ORIGINAL ARTICLE

STAT1 Mutations in Autosomal Dominant Chronic Mucocutaneous Candidiasis (14 pts/5 kindreds)

Frank L. van de Veerdonk, M.D., Ph.D., Theo S. Plantinga, Ph.D., Alexander Hoischen, Ph.D., Sanne P. Smeekens, M.Sc., Leo A.B. Joosten, Ph.D., Christian Gilissen, Ph.D., Peer Arts, Ph.D., Diana C. Rosentul, M.Sc., Andrew J. Carmichael, M.D., Chantal A.A. Smits-van der Graaf, M.D., Ph.D., Bart Jan Kullberg, M.D., Ph.D., Jos W.M. van der Meer, M.D., Ph.D., Desa Lilic, M.D., Ph.D., Joris A. Veltman, Ph.D., and Mihai G. Netea, M.D., Ph.D.

N Engl J Med 2011; 365:54-61 | July 7, 2011

Gain-of-function human *STAT1* mutations impair IL-17 immunity and underlie chronic mucocutaneous candidiasis

Luyan Liu[1], Satoshi Okada[2], Xiao-Fei Kong[2], Alexandra Y. Kreins[2], et al

J Exp Med 2011; 208:1635-1648 (47 pts/20 kindreds)

Defects Associated with Chronic Mucocutaneous Candidiasis

- Primary defects inhibiting Th17 generation or function
  - Deficiency in Th17 generation (STAT3 and Tyk2 [+DOCK8] defects)
  - Primary defects in IL17RA (AR) and IL-17F (AD) - interfere with IL17/22 signaling
  - STAT1 gain of function mutations (AD) - inhibit Th17 function
- CARD9 deficiency: failure to signal via dectin pattern recognition receptor pathway
- Secondary defect due to neutralizing autoantibodies to IL-17 and IL-22 in APECED/APS1
- The Th17 response with IL-17 and IL-22 production along with local response via pattern recognition receptors are critical in the host (mucocutaneous) defense to candida

" the greatest teachers of modern immunology: patients with immunodeficiency diseases."
Robert A. Good, M.D., D.Sc., Ph.D.

The "Complete Book of PIDD"
Is Still Being Written